REMARKS/ARGUMENTS

Applicants desire to submit further amendments to the claims and arguments to provide for the allowability of the claims in this Application.

In this respect, the claims withdrawn are 1, 2, 5, 15, 17, 18, 19 and 21.

The claims now cancelled are 3, 4, 6-14, 16, 20, 22, 23, 25, 33, and 34.

CLAIMS REJECTIONS- 35 USC 112

The claims now in this Application are 24, 26-32 and 35.

With respect to the '112 rejection, the new matter "at least 3mm in diameter" no longer appears in any pending claim.

INDEFINITE

The Examiner has stated that the claim 24 is unclear about the components of the claimed product and about the final properties of "tissue like organization of cells".

Claims 24, 26, 28, 29, 30, 31 are herein amended so as to bring clarity into the claims. The Applicant herein deletes the claims 33 and 34, as noted.

CLAIMS REJECTIONS 35 USC 102

Former claims 24-35 (prior to the filing of the RCE and the previous amendment) were rejected under 35 USC 102 (b) as being anticipated by US 5755814 (Berg et. al) in the last Official Action in the Parent Application.

The Examiner states that Berg et al discloses a preparation of dermal fibroblasts grown in a simple culture vessel, which teaches that fibroblasts attached to plastic dishes well and proliferated better without matrices. The Examiner contends that these are same cell preparation as the presently claimed cells of the present invention. Thus the cited patent anticipates the present invention.

The Applicant wishes to clarify that in the Berg patent, cells have been shown to have proliferated better without a matrix, on a plastic surface. But these cells, which have

proliferated better, have not formed a dermal tissue (which is the aim of the present invention): They have remained as monolayers which have no utility in any application onto skin wounds. Thus the cell preparation on plastic in the Berg invention is proliferating monolayers while the cell preparation in present invention is 3D dermal tissue. Therefore, the Berg patent does not anticipate that dermal tissue which can be formed by the macromass method on plastic as per the present application.

Whereas, the present application provides macromass constructs, which are tissue-like (unlike monolayers): the cells are integrated into a unified tissue like sheets as seen from the figures, so they have utility as a skin implant.

In the Berg invention and disclosure, the tissue like construct is made using a collagen matrix; while in the present application the macromass constructs are made without using any matrix. Thus, neither from the cells on plastic nor cells on matrix of the Berg patent can anticipate that dermal tissue can be made on plastic.

Hence, the desired result or end product of using only plastic dishes in the Berg's invention is optimal proliferation and attachment, whereas the desired end product of the present invention is dermal tissue generation.

The Examiner has further rejected claims 24-25 and 27-34 which claims are rejected under 35 USC 102(b) as being anticipated by Furukawa et al.

The Applicant herein gives the following clarification emphasizing the difference between the macromass constructs, which are macroscopic unified sheets and the Furukawa et al. aggregates which are separate minute clumps.

As presented in the Furukawa et al. paper itself, in order to form a unified construct of a sheet-like form from their aggregates, the aggregates have been attached into a mesh of polyglycolic acid. The polyglycolic acid mesh integrates or unifies the aggregates into a sheet-like form. Thus the Furukawa et al. aggregates are not formed up to the desired level for formation of sheets (which have more utility as a skin implant) and requires a supporting mesh to bring these aggregates together to form an organized tissue like sheet.

Unlike this, the macromass construct of the present invention is on its own a unified sheet-like form, with no mesh needed to hold together the cells. The Furukawa et al. aggregates cannot on their own form a unified sheet-like construct. This shows that the product of the present invention, the macromass construct is physically distinct from the Furukawa et al. aggregates.

The macromass constructs of the present application are more effective as a dermal tissue than the Furukawa et al. aggregates. The Furukawa et al. aggregates are 200-280 μm in diameter (0.02-0.028 cm), so by themselves they do not have application as an implant for the skin wounds: the small aggregates which are separate from each other would not remain in place on the wound by themselves and a single aggregate would cover an insignificant area of the wound. Numerous Furukawa et al. aggregates are required to cover a meaningful area and additionally they require to be held together by a support such as polyglycolic acid mesh to achieve the unified sheet-like property which is useful for application on skin wounds.

On the other hand, the macromass construct of the present invention is a unified sheet on its own and is about 3.0 cm in diameter when made in a 3.5 cm dish, so it is a more effective dermal tissue than the Furukawa et al. aggregates by themselves. This again highlights the fact that the macromass constructs are physically different from the Furukawa et al. aggregates.

Thus, the Furukawa et al. paper actually teaches that in order to make a construct that would be useful as a skin implant, one needs to use a mesh such as polyglycolic acid to entrap the cell clumps and hold them together. Thus it can by no means be anticipated from the Furukawa et al. paper nor is it obvious from the disclosure and teachings in that paper that effective dermal tissue can be made without the aid of a supporting mesh, which has been achieved by the macromass method of the present invention.

Further, the reference by Furukawa et al. discloses a tissue like organization of cells that are separated small aggregates. The product of the present invention is a unified macroscopic sheet. The present application has formed a tissue construct without any

tissue forming agents such as insulin, dexamethasone and basic fibroblast growth factor and without the rotational tissue culture technique.

In view of the seeding density, the Applicant wishes to delete the words" at least 3mm in diameter", and this has been done. The Applicant wishes to clarify the final components of the product of the present invention by amendment of the claims. The Applicant further wishes to delete the claims 33 and 34, which has been done.

There would have been anticipation if all the limitations are covered by the cited reference. The Applicants herein give the claims as a tissue like constructs and not aggregates as formed in the cited reference. Minute separate aggregates cannot be taken as tissue like sheet wherein the present application has formed a unified sheet as evident from the figures.

The cited reference of Furukawa et al has focused on the spheroids from human dermal fibroblasts. In their article, it is mentioned that the formation was possible with improved cell culture conditions such as inclusion of insulin, dexamethasone and basic fibroblast growth factor as well as rotational shaking to promote aggregation. They have also stated that the shape of the aggregates varied with time of rotational culture. They could attain the spheroids as per their definition only after 24 hours. The authors had obtained aggregates in irregular shape after 12 hours and then because of rotational shaking they could obtain the spheroidal aggregates. Hence, the product obtained was different at the end of 12 hours and the final form of spheroidal aggregates could be obtained as a result of shaking after 24 hours.

In the present application the inventors have obtained a tissue like sheet (which is dissimilar to the Furukawa et al. aggregates as desired earlier) after or within four (4) hours. The tissue like sheet could be achieved solely with the aid of high cell density and without the influence of external agents.

The Examiner has contended that the cited reference describes the fibroblasts cells grown by shaking or by rotational culture ends in the same three dimensional tissue like organization of cells. In addition to the distinct differences as described above, the

Applicant wishes to state there needs to be a common factor to find out for comparison. The Examiner has given little importance to the type of the culture technique.

There is no anticipation nor suggestion nor motivation in the cited reference of Furukawa et al. that one can get the tissue like formation (aggregates) only with the high cell density seeding without the specific tissue culture conditions and rotational culture.

CLAIMS REJECTIONS 35 USC 103

Claims 24-35 are rejected over US patent 5755814 (Berg et.al.) and Furukawa et al.

Thus the inventors wish to reinstate their views and wish to request the Examiner the following response in addition to the earlier response wherein the Applicant has provided a comparative table.

In case of Berg et al., the reference has used matrix free cell preparation as a control. However, the cited patent has used PLASTIC dishes coated with poly lysine which has influence on the cell- adhesion. As per the cited patent the PLASTIC used in the specification therein is polylysine coated plastic tissue culture dish. (Column 3- line 2). It is known that Poly-Lysine enhances electrostatic interaction between negatively-charged ions of the cell membrane and positively-charged surface ions of attachment factors on the culture surface. When adsorbed to the culture surface, it increases the number of positively charged sites available for cell binding. Hence the entire aim of the plastic dish in the cited reference was to have cell culture surface wherein the cells cultured and proliferated well so that it can be used as a control for the experiments to compare with growth on the collagen matrix.

However, the cited reference in fact does not state that plastic dish without polylysine coating would be sufficient for the dermal tissue formation or a three dimensional aggregation of cells. In fact the cited reference has used the coated plastic dish as a control to compare the results with collagen matrices. Hence one uses a control for representing the base line condition for comparing with test conditions.

The Examiner contends that Berg et al. teaches inoculation of dermal fibroblasts grown in the absence of matrix and that it is obvious for one to combine the cell mass grown at high cell density as in Furukawa et al. to obtain tissue sheets.

The Applicant wishes to convey that the cell culture prepared in Berg et al. is with poly lysine coated plastic dishes wherein simple monolayers are formed and not tissue like constructs. There is no obvious teaching in Berg's et al. patent that three dimensional tissue like sheets can be made without plastic coated dish in absence of matrix.

And further even though Furukawa et al. has not used the treated plastic dishes they have used cell culture conditions such as inclusion of the insulin, dexamethasone and bFGF in the cell culture for aggregate formation, these factors (as mentioned in the page 442 column 2, end of first paragraph) potentiate the secretion of extracellular matrices and promote the formation of aggregates, the cited reference of Furukawa et al. as inferred by the Applicant makes use of extraneous tissue forming agents for formation of aggregates. These agents are not used in the present application. Furukawa et al. have used polyglycolic acid mesh which entraps the aggregates to make a unified construct. Hence there is no obvious teaching that unified sheet like constructs can be made without a supporting mesh.

Thus, in case of BERG et al. the end product is a monolayers of cells which just adhered to the plastic dish and was demonstrated to proliferate well whereas the present application has provided a dermal tissue sheet is three dimensional arrangement of cells. In case of Furukawa et al. the end product is a minute separate aggregates of cells or spheroids whereas the present invention is a tissue like construct made by unified integration/ organization of cells. The structures/ product formed by Furukawa et al. procedure is with the aid of tissue promoting agents and rotational culture and that the product obtained by the present invention is solely due to high cell density. The tissue construct which is a unified sheet is formed within 4 hours as against the minute separated cell aggregates formed in 24 hours by Furukawa et al.

In addition to the above detailed response to the final official action in the parent application, the Applicant hereby specifically has addressed the particular points of the Examiner by inserting the corresponding replies (as underlined text) for the respective objections raised by the Examiner. It should be noted that this paper contains a further response to the points raised in the final office action in the parent application of the RCE dated September 28, 2006.

1. Referring to the page 5, second paragraph related to Berg et al. patent, the Examiner has referred to the fibroblasts grown on plastic as "sheet like uniform layer of cells".

The Applicant wishes to clarify that the cells on the plastic in the Berg et al. patent are not a three-dimensional sheet like layer of cells as contended by the Examiner. The Berg patent nowhere describes the cells on plastic as a three dimensional sheet. They are only monolayers of cells, which cannot be lifted as a sheet. Hence it cannot be called as "sheet like". If it is attempted to be lifted, the monolayers of cells will only scraped and individual cells will come off from the plastic.

2. Referring to the page 5, second paragraph wherein the Examiner has referred to the cell seeded on plastic as a "final cell mass".

In response to this, the Applicant wishes to state that in addition to above point 1, the monolayers on plastic cannot be picked as a unified cell mass.

3. Referring to the page 5, second paragraph, the Examiner has given the diameter of plastic wells as 0.9 cm and the density been calculated based on that.

The Applicant wishes to convey that in the Berg et al. patent the plastic dishes that have been used are 24 well plate (column 9 line 40 and 41) where the diameter of one well is 1.55 cm, which provides for an area of 1.9cm^2 for each well. Berg et al. have given 0.9 cm as the diameter of the matrix (not the well) used which was placed in the 24 well plate. Therefore, 4.8 x 10^5 cells /cm^2 as calculated by the Examiner has been used on the matrix and not on the plastic well.

Hence, it cannot be anticipated or obvious to use such a density without a matrix, which is main claim of the present invention. The present invention uses a higher cell density on plastic without any matrix. In the Berg et al. invention on plastic in 24 well plate without any matrix, the cell density is 1.57 $x10^5$ cells /cm^2 (3 x 10^5cells / 1.9 cm^2).

4. Referring to the page 5 second paragraph, relating to the teachings of the Berg et al. patent to use a matrix as encompassed by the present claim 33 and 34.

In order to remove the ambiguity of the claims the Applicant has now deleted the claims 33 and 34.

5. Referring to page 6-second paragraph related to Furukawa et al. reference wherein the Examiner has considered the cell preparation as a "whole" within the culture vessel.

The Applicant intends to point out that the physical nature of the cell preparation even when considered as a whole is different from the present invention (minute separate aggregates compared to the single unified tissue like sheet in which all the seeded cells are integrated).

6. Referring to page 6-second paragraph related to Furukawa et al. reference wherein the Examiner has calculated the cell density and has contended that initial cell seeding density of the cited cell preparation falls within the claimed range.

The Applicant wishes to emphasize that although using a similar density, Furukawa et al. are subjecting the cells to rotational culture and tissue-forming agents following cell seeding, so they are obtaining a different product than the present invention as reiterated several times. Thus, it cannot be anticipated that a single unified sheet-like construct can be obtained by means of high cell seeding density alone, which is the main claim of the present invention.

7. Referring to page 6, third paragraph, wherein the Examiner has stated that the final product of Furukawa et al. is a 3- dimensional tissue like organization as the claimed product.

The Applicant wished to restate that although both the products are three (3) dimensional organization, but as the Applicants have described above in the preceding the paragraphs, the physical nature or characteristic of the Furukawa et al. organization of cells is distinctly different from the unified sheet like organization of the present invention.

8. Referring to page 6, third paragraph, the Examiner has stated that claimed invention does not exclude supplements such as insulin, dexamethasone.

The Applicant wishes to bring to the attention of the Examiner that the present claims does state "without the aid of tissue forming agents" which includes such and other supplements. If the Examiner desires a different limitation, she is respectfully asked to call Applicants' attorney to do what is necessary to take care of this matter.

9. Referring to the page 7, the first and second line, the Examiner has stated that the final components of the claimed invention have not been defined.

The Applicant wishes to clarify that the product of the present invention has been defined as a single, unified, macroscopic construct wherein all the seeded cells have been integrated into one unit; which distinguishes the physical nature of the macromass construct from the Furukawa et al. aggregates.

10. Claims rejections 103, page 8, the Examiner has stated that it is obvious to combine the cell preparation (initially made without matrix) with a matrix as done by Furukawa et al.

The Applicant wishes to delete the claims 33 and 34.

11. Referring to page 8, second paragraph the Examiner has stated that the density of 4.8×10^5 cells / cm^2 has been used in the absence of matrix.

The Applicant wishes to convey that as given in point 3 above, the cited density has been used on matrix and not on the plastic dish. In the Berg et al. invention, the density used on plastic without matrix is below the range of the present invention.

12. Referring to the page 9, relating to the comments of the Examiner to our previous arguments, in the second paragraph, the Examiner has interpreted the Berg et al. patent to have a well diameter of 0.9cm. The Examiner contends that the arguments are not persuasive.

We again convey and specifically point out that Berg et al. have given 0.9 cm as the diameter of the matrix, not of the well. The 24 well plate has diameter of 1.55 cm, so that the cells on plastic without matrix are at a lower seeding density than the range of the present invention.

If the specific arguments to overcome the points raised or mentioned by the Examiner are not considered persuasive, it is still respectfully maintained by the Applicant that the product of the present invention is distinct and clearly patentably different, because the cells on plastic in the Berg et al. patent are monolayers, while the construct is on a collagen matrix, whereas, the present invention is a construct on plastic. These are patentable structural features and differences.

13. Referring to the page 9, relating to the comments of the Examiner to our previous arguments, in the third paragraph, wherein the Examiner has considered that the Furukawa et al. aggregates as a whole mass in the dish.

The Applicant has already argued and specifically pointed out that the whole mass collected from the dish is not of the same physical nature as the macromass construct. Another clear patentable feature.

If there are any points outstanding, the Examiner is respectfully asked to call Applicants' attorney to do what is necessary to place this Application into condition for allowance.

If any fees are necessary, please charge to our Deposit Account No. 50-3108. If for any reason there are insufficient funds in the Deposit Account, please charge to Deposit Account No. 10-0100.

Early and favorable reconsideration is respectfully solicited.

Respectfully submitted,

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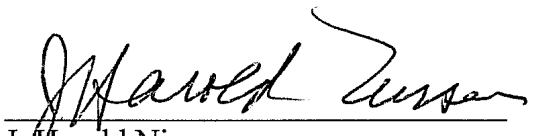
By: 

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